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FINAL CLINICAL SUMMARY

DOSING-RANGE STUDY OF MS CONTIN 30 MG TABLETS IN PATIENTS WITH CHRONIC PAIN

PROTOCOL NO. 84-0101

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ABSTRACT

Twenty-four (24) of thirty (30) cancer patients completed this dosing-range study with dropouts not attributable to MS Contin. The study was designed to reflect a real clinical situation in which an analgesic is titrated to a level achieving adequate analgesia with acceptable side effcts. Patients had previously been prescribed a narcotic analgesic and, overall, these encompassed many of the commonly used narcotics. Regardless of the particular opioid previously used, each patient was successfully converted to MS Contin q 12 h or q 8 h. It was found that these patients could go from an immediate-release morphine sulfate preparation doses q 4 hours to a MS Contin regimen doses q 12 h or q 8 h with the majority of patients maintained on a q 12 h regimen if adequate total daily amount of morphine sulfate as MS Contin would be given.

The clinical impression of the Investigator was that MS Contin was at least better regarding analgesia compared with their previous analgesic. The Investigator also felt that half the patients manifested at least fewer side effects compared with their pre-study narcotic. These findings based on a realistic therapeutic study design support the safety and efficacy of MS Contin 30 mg Tablet for the prolonged relief of severe pain when dosed q 12 h with proper dosage adjustment to this twice daily regimen.

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I INTRODUCTION

It is generally accepted that routinely scheduled analgesic dosing is the preferred treatment of chronic pain in patients with cancer.[1-4] However, despite the wide array of narcotic analgesics previously available for general use no one product approached that of the ideal analgesic. Ideally, an analgesic preparation, used for the treatment of chronic pain, should meet the following criteria:

A. Be orally effective

B. Permit a dosing regimen that is convenient to the patient

C. Prevent breakthrough pain

D. Produce prolonged effective drug levels

E. Be devoid of accumulation properties

Methadone might be considered as a drug that approaches that of the ideal narcotic analgesic for chronic pain management. Unfortunately, methadone, because of its long half-life (24-57 hours) and accumulation potential is not without its difficulties.[5]

MST Continus Tablets, a controlled-release morphine sulfate tablet widely used in Europe, was proven to be an ideal narcotic analgesic for the treatment of chronic severe pain. In European studies MST Continus Tablets have been shown to be orally effective, convenient to use (i.e., can be dosed every 12 hours), prevents breakthrough pain (i.e., analgesia can last 12 hours), produces steady morphine plasma concentrations, and does not accumulate with continued dosing.[6-11] The American formulation called MS Contin 30 mg Tablet is equivalent to MST Continus 30 mg Tablet and is now available as a prescription medication.

II OBJECTIVE

The purpose of this study was to confirm the European experience, namely, that MS Contin 30 mg Tablets as with its equivalent MST Continus 30 mg Tablets, are safe and effective for prolonged relief of severe pain when given as a q 12 hour regimen. The study evaluated MS Contin in a realistic

setting in which the drug was titrated to achieve adequate analgesia with minimal side effects. Via a dosing-range protocol designed to have statistical sensitivity, a spectrum of maintenance doses of MS Contin 30 mg Tablets was determined for cancer patients requiring narcotic analgesia.

III MATERIALS AND METHODS

A. Subjects

Participants in this study were cancer patients of either sex above the age of 18 years who were deemed candidates for narcotic analgesics for control of their pain. Eligibility criteria were structured so as not to exclude the wide range of cancer pain syndromes existent in this patient population. However, patients had to exhibit the characteristics of being compliant, rational, reasonably responsive, and capable of subjective evaluation. Such patients had to express a willingness to follow protocol requirements as evidenced by written informed consent. Excluded were patients who had manifested hypersensitivity to morphine products. Those who had major organ dysfunction which might adversely affect safety or obscure efficacy were excluded from the study. Reclusive living circumstances was also an exclusion criterion for safety reasons.

B. Medications

1. Test

MS Contin 30 mg Tablets, Lot No. CB11-35. [MSC]

2. Reference

Morphine Sulfate 15 mg Tablets, Roxane, Lot No. 830634 [IRMS]
Morphine Sulfate 15 mg Tablets, Lily, Lot No. 8DA96A [IRMS]
Morphine Sulfate 30 mg Tablets, Lily, Lot No. 8CU32A [IRMS]

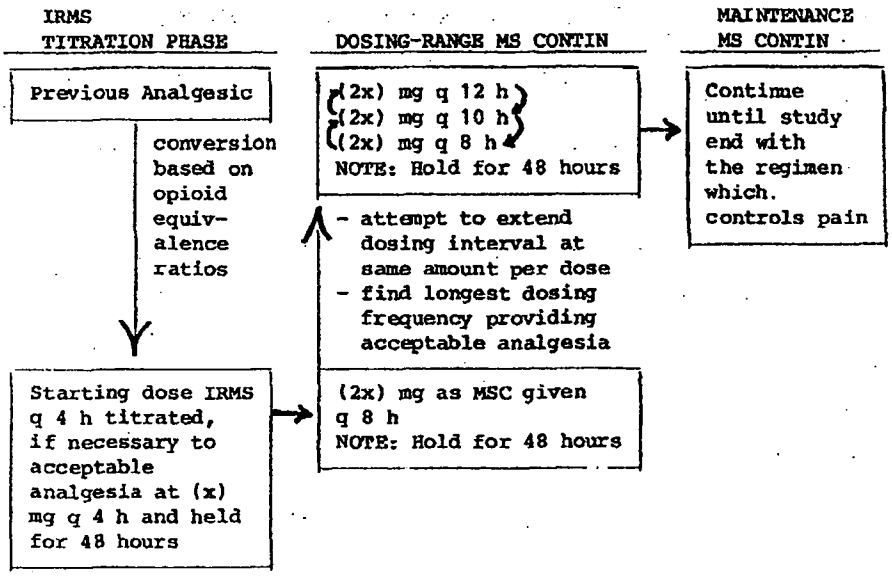
C. Trial Phase

1. Design

This was a controlled, crossover (sequential), open-label, dosing-range study lasting from 10 days to four weeks at the discretion of the Investigator.

2. Procedure

The study concept is diagrammed as follows:



NOTE: It was expected that a number of patients stabilized on MSC (2x) mg q 8 h would not be adequately controlled when switched to MSC (2x) mg q 12 h. This plan provided a measure of sensitivity; that is, patients overall required morphine sulfate at approximately the daily dosage found as the Maintenance regimen.

a. IRMS Titration Phase

Patients were converted from their previous opioid analgesic to immediate-release morphine sulfate at 15 or 30 mg q 4 h based on standard opioid equivalence ratios.

If not obtaining adequate analgesia at IRMS 15 mg q 4 h patients, after 24 hours, were switched to IRMS 30 mg q 4 h. Continued daily updosing was done until adequate analgesia was achieved or side effects prevented an increase in dose.

When adequate analgesia was obtained for at least 48 hours on IRMS, the patient was instructed to begin MS Contin as described in the "Dosing-Range" Phase which follows.

b. Dosing-Range Phase

Patients were begun on MSC q 8 h at double the dose of IRMS determined in the IRMS Titration Phase. The attempt was then made to extend the dosing interval up to q 12 h while not increasing the amount of MS Contin given per dose.

Patients were held at each level for approximately 48 hours before changing to a longer dosing interval. Inadequate analgesia at any level resulted, after 24 hours, in a patient returning to the previous dosing level and one additional attempt made to extend the dosing interval.

c. Maintenance Phase

Patients were maintained on MSC at the final dosing regimen determined in "b" for the duration of the study specified by the Investigator up to a maximum of four weeks for the entire study. If patients experienced inadequate analgesia during the Maintenance Phase they were returned to the previous dosing level and dose adjusted until a stable regimen was determined. The Maintenance Dose of MSC was defined as the minimal dosing regimen (amount and frequency) providing acceptable analgesia and acceptable side effects for at least two days.

3. Evaluations

Usual Demography and Medical Background were reported. Physical Examination, Hematology, Chemistries and Urinalysis were optional but recommended.

a. For Efficacy

i Immediate-Release Morphine Sulfate Tablet Titration Data

ii Telephone Assessments were done periodically

iii Daily Patient Record was optional

iv Investigator's Record of Dosing-Range and Maintenance Phase Data

v Investigator's Summary of Study

b. For Safety

Adverse experiences, whether spontaneously reported or elicited upon direct questioning, were recorded and evaluated promptly by the Investigator's to determine the severity, duration, initiation of corrective measures, if warranted, and subjects followed with "normal".

IV RESULTS

A. Background

Thirty (30) cancer patients were entered and twenty-four (24) completed the study. Their oncologic diagnosis, age and gender are given in Table 1. The six dropout patients were discontinued for a variety of reasons none related specifically or solely to MS Contin (see Table 1).

B. Efficacy Evaluations

Table 2 displays the maintenance dose of the previously narcotic analgesic the 24 patients who completed the study required for pain control. Juxtaposed are the maintenance doses of MS Contin 30 mg Tablets which were found by range-dosing to be adequate to control their pain.

In Figure 1 a comparison is made of the analgesic equivalence of MS Contin and immediate-release morphine sulfate. Each patient was titrated to acceptable analgesia with IRMS. Then they were switched to MS Contin and a maintenance dose of this controlled-release preparation was determined via the dose ranging format described in Section III.C.2. Thus, Figure 1 demonstrates that patients maintained on a q 4 hours morphine sulfate regimen under the constraints of

protocol design could adequately be maintained on a q 12 h to q 8 h MS Contin schedule. It must be emphasized that the design employed in this study negatively biases the potential efficacy of the q 12 hour schedule. That is, patients were switched to MS Contin first on a q 8 hour program. They were then tested at q 12 hours but using the same amount of morphine sulfate per dose thereby decreasing the total daily amount of morphine sulate. Consequently, those patients on the q 12 hours schedule gained not only the benefit of decreased dosing frequency, but it was also possible to decrease the total daily amount of morphine required to achieve the same analgesia as obtained with the immediate-release morphine preparation given q 4 hours. These findings are quantified in Table 3. That is, 57% of patients tried on the q 12 h regimen were successfully controlled and irrespective of the MSC regimen a significant reduction (18.6%) in the daily morphine requirement was found relative to MSIR regimen.

Table 4 shows a global evaluation by the Investigators of analgesic potential of MS Contin compared with the previous narcotic the patients were prescribed. In all cases in the judgment of the Investigators, MS Contin provided the patients superior or better analgesia than did their previous analgesic.

C. Safety Evaluations

As can be seen in Table 4 it was the opinion of the Investigator that approximately half of the patients had fewer side effects with MS Contin compared with their pre-study analgesic. No patient had side effects which were greater for MS Contin than for their pre-study analgesic. The actual untoward reactions reported for MS Contin were those usual for morphine and included, in part, lightheadedness, nausea, dizziness, constipation and anorexia. Those reactions considered notable and reported as adverse reactions were few and shown in Table 5.

D. Sensitivity of Experimental Procedure

One measure of the discriminatory ability of an experimental method is obtained by observing the effect of changing dosage.

Thus, if all of a group of N patients perform satisfactorily at dose D_0 and the dose is reduced to D_1 and the percentage of satisfactory responses drops from P_0 to P_1, we may view the experimental procedure as being sensitive. Further, if P_1, although less than P_0, is still large enough to be clinically useful, we may regard the dose D_1, as being a clinically useful dosage.

In this study all 24 patients were controlled when placed on (x) mg IRMS q 4 h. All patients had their pain similarly controlled when given MSC at (2x) mg q 8 h. However, when the dosing interval was extended to q 12 h while maintaining each dose at (2x) mg, 57% of the patients continued to respond satisfactorily regarding pain relief. This was a significant reduction ($p \sim 0.05$) from 100% and therefore the assay was deemed senstive.

V SUMMARY AND CONCLUSIONS

Twenty-four (24) of thirty (30) cancer patients completed this dosing-range study with dropouts not attributable to MS Contin. The study was designed to reflect a real clinical situation in which an analgesic is titrated to a level achieving adequate analgesia with acceptable side effects. Since MS Contin 30 mg Tablet is equivalent to MST Continus 30 mg Tablet, the European experience with the British tablet should be paralleled by that of MS Contin. This hypothesis was confirmed with all completed patients achieving acceptable pain relief on a q 12 hour or q 8 hour dosing regimen with MS Contin 30 mg Tablet(s). Patients had previously been prescribed a narcotic analgesic and, overall, these encompassed many of the commonly used opioids. Regardless of the particular narcotic previously used, each patient was successfully converted to MS Contin q 12 h or q 8 h. Of note, half the patients were maintained on a q 12 h regimen in spite of the study design which resulted in a decreased total daily amount of morphine sulfate when the patient was placed on the q 12 hour program. This is of increased significance since all patients had been titrated on an immediate-release morphine sulfate tablet given every four hours. Thus, these patients could go from an immediate-release morphine sulfate preparation dosed q 4 hours to a MS Contin regimen dosed q 12 h or q 8 h with the majority of patients maintained on a q 12 h regimen if adequate total daily amount of morphine sulfate as MS Contin would be given.

The clinical impression of the Investigator was that MS Contin was at least better regarding analgesia compared with their previous analgesic. The Investigator also felt that half the patients manifested at least fewer side effects while on MS Contin with no patients having greater side effects compared with their pre-study narcotic. These findings based on a realistic therapeutic study design support the safety and efficacy of MS Contin 30 mg Tablet for the prolonged relief of severe pain when dosed q 12 h with proper dosage adjustment to this twice daily regimen.

JJS/msd

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TABLE 1

ONCOLOGY - PATIENT DEMOGRAPHY

Disseminated ovarian carcinoma, 46 y/o, F	Renal cell carcinoma c bone and lung metastases, 37 y/o, M
Recurrent cervical cancer, 57 y/o, F	Squamous cell carcinoma of head and neck, 64 y/o, M (5*)
Vulvar carcinoma c pubic bone metastases, 56 y/o, F (1*)	Multiple myeloma, 61 y/o, M
Adenocarcinoma of Lung, 53 y/o, M	Ovarian carcinoma, 76 y/o, F
Small cell lung carcinoma, 51 y/o, M	Carcinoma of cervix, 42 y/o, F
Adenocarcinoma of sigmoid colon, 67 y/o, M	Metastatic breast cancer, 46 y/o, F
Recurrent ovarian carcinoma, 48 y/o, F	Metastatic nonsclerosing Hodgkin's Lymphoma and sarcoma, 38 y/o, F
Metastatic prostatic carcinoma, 72 y/o, M (2*)	Carcinoma of cervix, 31 y/o, F (6*)
Carcinoma of cervix, 58 y/o, F	Multiple myeloma c bony metastases, 64 y/o, F
Diffuse histiocytic lymphoma, 56 y/o, F	Histiocytic lymphoma, 54 y/o, F
Adenocarcinoma of lung c brain and skin metastases, 57 y/o, M	Carcinoma of the colon, 54 y/o, F
Adenocarinoma of Lung, 69 y/o, M	Carcinoma of the lung, 63 y/o, F
Diffuse histiocytic lymphoma, 36 y/o, M (3*)	Carcinoma of cervix c intra-abdominal dissemination, 61 y/o, F
Metastatic ovarian carcinoma, 48 y/o, F	Metastatic osteosarcoma, 64 y/o, M
Carcinoma of the cervix c pelvic involvment, 50 y/o, F (4*)	Carcinoma of Lung c diffuse metastases, 65 y/o, F

1*Patient unable to be stabilized on IRMS at 15 or 30 mg q 4 h and was discontinued.
2*Patient was discontinued due to family objections to patient sedation which was attributable to IRMS or other medications.
3*Patient was discontinued due to development of pneumona after 24 h on study.
4*Patient was discontinued due to intractable nausea/vomiting while on IRMS.
5*Patient was discontinued due to confusion and disorientation secondary to brain metastasis.
6*Patient was discontinued due to intractable nausea/vomiting on both morphine preparations.

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TABLE 2

EFFICACY EQUIVALENCE OF MS CONTIN COMPARED WITH PREVIOUS NARCOTIC

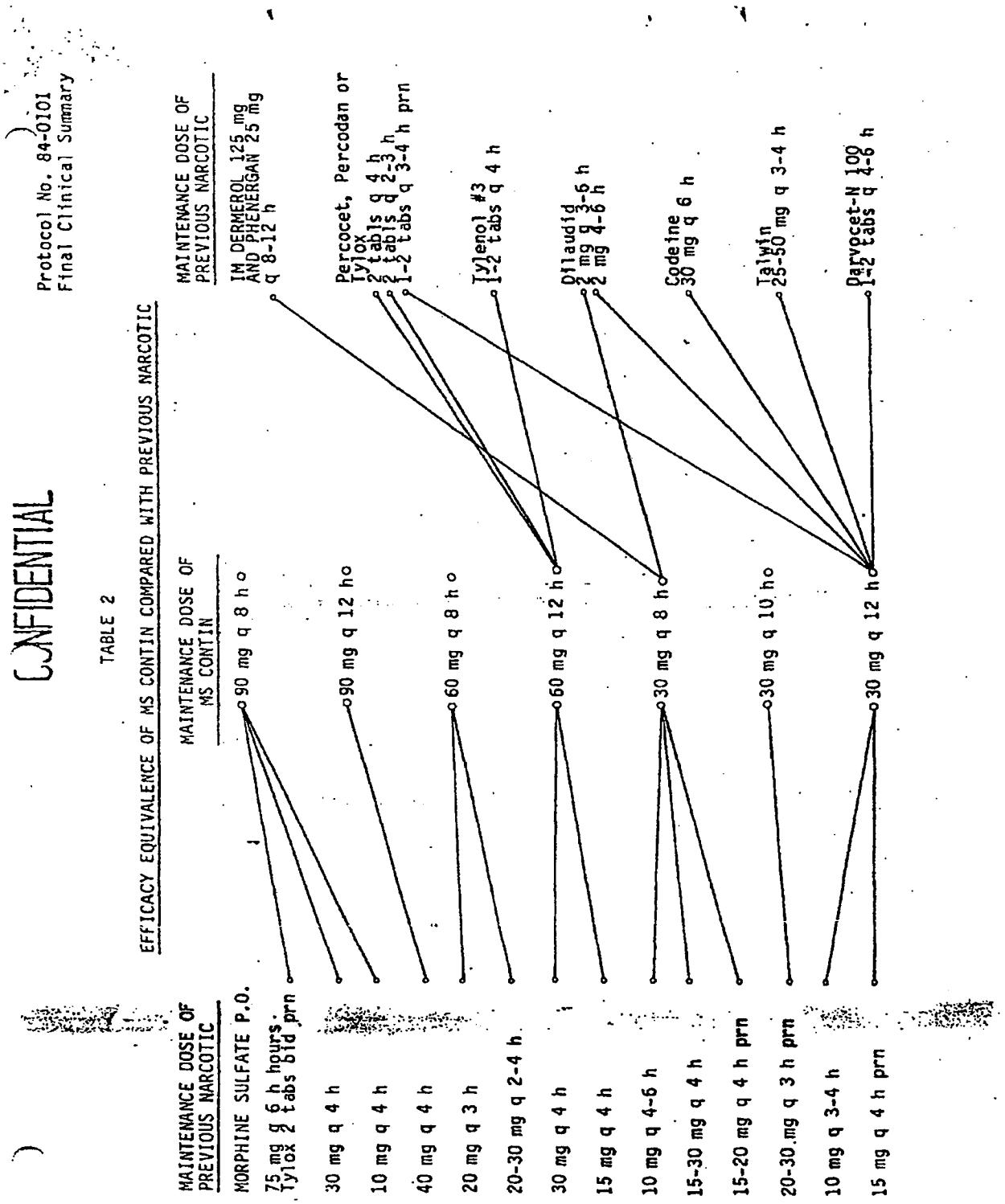

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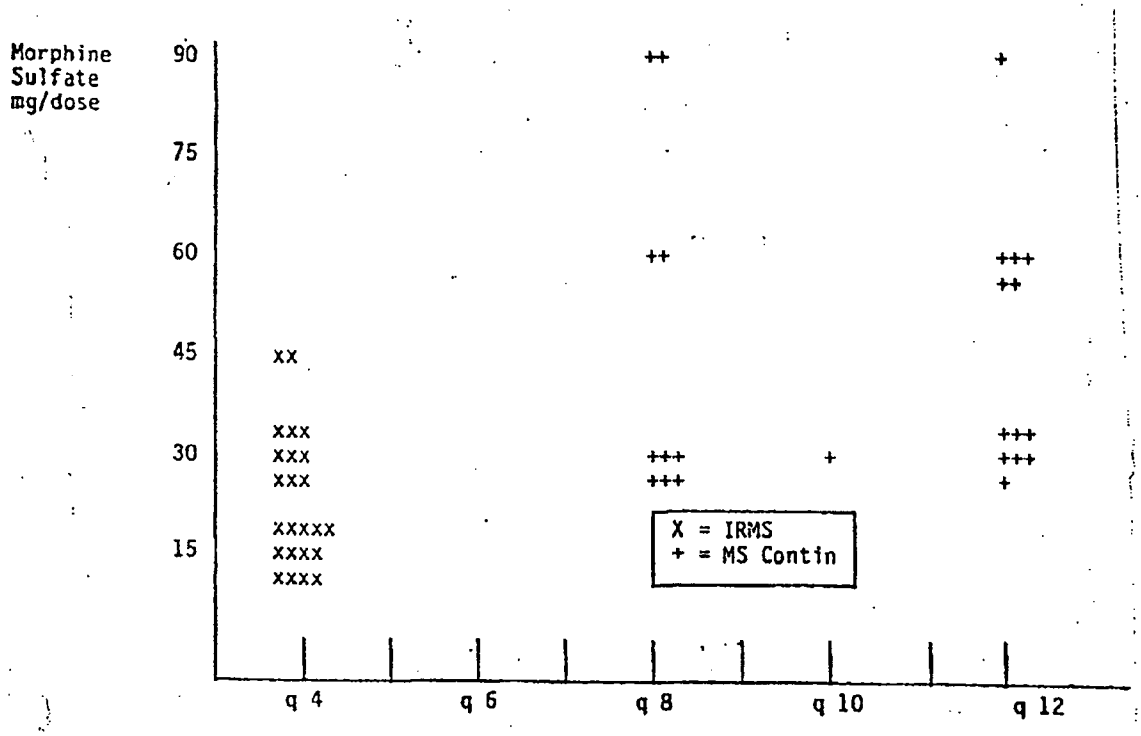
FIGURE 1

EFFICACY EQUIVALENCE OF MS CONTIN COMPARED WITH IMMEDIATE-RELEASE MORPHINE SULFATE (IRMS)



Patients were titrated on IRMS over a period lasting of 2.8 days (range of 2-10 days) and stabilized on (x) mg q 4 h. They were then switched to MSC at (2x) mg q 8 h with subsequent dosing interval extention to (2x) mg q 12 h which resulted in a decrease of total daily amount of morphine sulfate taken. Consequently, 43% of the patients could not be controlled at this lower daily dose attesting to the sensitivity of the study design. The final MSC regimen providing adequate pain prevention is shown above as + with the mean duration on MSC being 14.4 days (range 3-28 days). Presumably, nearly all patients would have achieved adequate pain control if MS Contin was dosed at an equivalent daily amount of morphine sulfate as was given for IRMS, that is, MS Contin (3x) mg q 12 h.

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TABLE 3

MORPHINE REGIMEN DATA

Frequency of MSC	N
q 8 h	10
q 10 h	1
q 12 h	13

FREQUENCY OF SUCCESS FOR PATIENTS TRIED ON MSC AT Q 12 H

q 12 h	N	
successes	13	57%*
attempted	23	
not-attempted	1	

(due to progression of disease one patient was never tried at q 12 h regimen)

	AVG. TOTAL DAILY DOSE	S.E.	AVG. # OF DAYS ON DRUG
MSIR	138.8 mg	12 mg	2.8
MSC	113 mg	13 mg	14.4

Dose Reduction 18.6% $p < .01$

*Note: When attempted at q 12 h patients continued to receive same amount of MSC per dose; therefore, all patients placed on the twice daily regimen received 2/3 of the total daily amount of morphine sulfate which successfully controlled pain when dosed q 8 h. Thus, failures were expected when patients were extended from MSC q 8 h to MSC q 12 h.

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TABLE 4

GLOBAL EVALUATION OF ANALGESIA AND SIDE EFFECTS

Investigator's Global Evaluation of MS Contin Compared With Patient's Previous Analgesic (Numbers refer to sum of patients placed in each category)

I ANALGESIC INFORMATION: MS Contin compared to the patient's previous analgesic is

Superior = 5, Better = 19, Same = 0, Inferior = 0

Therefore, the % Better or Superior = 100%
Random distribution of the analgesic rating would most likely have been split as 1/3 superior or better, 1/3 same as and 1/3 inferior to.
This difference is highly significant (z statistic 4.60, P < .0001)

II SIDE EFFECT EVALUATION:* MS Contin compared to the patient's previous analgesic has

Very few side effects = 6 Few side effects = 6
Same side effects = 11, More side effects = 0

Therefore, the % very few or few = 52.2%
Random distribution of the side effect rating would most likely have been split as 1/3 very few or few, 1/3 same as and 1/3 more side effects.
This difference is not significant (z statistic 1.02, P = .30) although the clinical advantage is clearly evident.

*NOTE: THE SIDE EFFECT EVALUATION could not be made on one patient due to potential that side effects noted on study were caused by concomitant medication.

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TABLE 5

ADVERSE REACTIONS

Five patients reported adverse reactions (two out of 30 in the IRMS phase: 6.7% and three out of 26 in the MS Contin phase: 11.5%). They were primarily gastrointestinal as follows:

Patient No.	AR with MSIR
16	Dizziness and hot flashes
30	Nausea and vomiting

Patient No.	AR with MSC
31	Nausea and vomiting
194	Nausea and vomiting
195	Nausea and vomiting